analog. To give a concrete example, if a stimulus was flashed 10′ up (in retinal coordinates) and an intervening eye movement carried gaze 10′ to the left, the post-movement location of the stimulus with respect to current gaze would be 10′ up and 10′ to the right. If spatial updating were to occur, what should it look like?

Prior studies of the superior colliculus and allied cortical visuomotor areas suggest that, if the intervening movement were a saccade, activity within the 'visual' map would jump to a new location to represent the goal's updated location with respect to gaze, *even though the stimulus itself is no longer visible* [1–4,6–11,16]. But what happens when the movement is not discrete or fully specified at the time of its initiation? Rather than jump, can activity within 'visual' maps migrate to represent the instantaneous, moment-to-moment location of a visual stimulus' *memory trace* with respect to a continuously changing gaze? Indeed, Dash and colleagues [5] infer that this is precisely what happens. They report that individual visually-responsive superior colliculus neurons became active precisely at the point in the pursuit eye movement trajectory when the excursion would have brought the originally-flashed stimulus (if it were still present) into the neuron's receptive field.

Remarkably, these neurons behaved as if the visual stimulus were still present and being swept through their receptive fields as the eyes moved! Extrapolating to the population of neurons, Dash *et al.* [5] thus posit the existence of a continuously migrating 'hill' of superior colliculus activity whose position at any point in time represents the location of a previously viewed stimulus in gaze coordinates. Their data may be the first empirical evidence that continuous spatial updating can be accomplished within the framework of a dynamic topography, a form of representation that could represent a general strategy for providing motor circuits access to the *right* information at the *right* time.

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Developmental Biology: Hedgehog Turns Into a Metabolic Hormone

The molecule Hedgehog is well known as an organizer of tissue morphogenesis. A recent report now demonstrates that it also plays the role of a gut hormone, orchestrating the nutrient response during fly development.

Neha Agrawal[1,2,3] and Pierre Léopold[1,2,3,*]

"*The fixity of the internal milieu is the condition for a free and independent life*" wrote Claude Bernard, the pioneer of homeostasis, in a posthumous book published in 1878 [1]. Homeostasis is not only key during adult life, but also during the energy-intensive processes of development. Homeostasis relies on the dynamic interactions between 'sentinel' tissues that sense variations in environmental conditions and the rest of the body where adaptations take place.

In recent years, studies using the fruit fly *Drosophila* have provided many insights into the interaction between such body systems, revisiting major paradigms in physiology with the use of efficient genetic approaches. One particular focus for this emerging field of 'genetic physiology' is the regulation of body growth, a developmental process that relies both on intrinsic (genetic) and extrinsic (environmental) parameters. Studies using flies have recently contributed to our understanding of the complex regulatory network allowing adaptation of the growth program to changes in nutrient availability [2].

Growth in flies is confined to a 4-day larval feeding period, when there is a spectacular 300-fold increase in body mass. This phase is critical since larvae subsequently enter a non-feeding maturation phase (or metamorphosis) before emerging as adults. Therefore, similar to humans, adult size is fixed at the end of the juvenile period. The extent of larval growth is largely dependent on the diet, particularly amino acids. With moderate diet restriction, larvae develop slower, reach a reduced size at maturation and give rise to small but well-proportioned adults. Diet acts on two hormonally controlled parameters to modify final body size: the larval

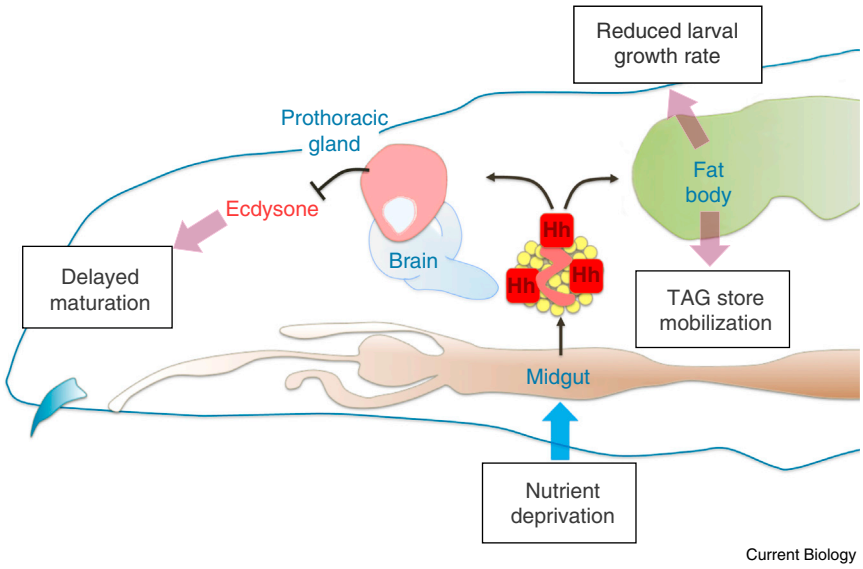

Figure 1. Nutritional regulation of systemic growth and developmental timing by humoral Hh.
Under conditions of nutrient deprivation, Hh is released from the larval midgut and circulates in the hemolymph bound to lipoprotein particles. Circulating Hh can independently activate Hh signaling in the fat body and the prothoracic gland. In the fat body Hh signaling slows larval growth and mobilizes triacylglycerol (TAG), while in the prothoracic gland it inhibits ecdysone production and delays maturation. The combined action of Hh on the fat body and the prothoracic gland allows the coupling of systemic growth and developmental timing and helps the animal respond to changes in nutrient availability.

growth rate and the duration of the larval growth period. Similar to most animal species, insulin/insulin-like growth factor hormones mediate the coupling between nutrient availability and the body growth rate, while the transition from juvenile to adult is mediated by steroid hormones (ecdysone in insects). Growth–diet coupling involves crosstalk between the endocrine organs that produce these hormones and the sentinel tissues that sense nutritional variations. Understanding the physiology of this complex regulatory network requires humbly walking on Claude Bernard's path and getting a clear description of organs and signals involved in this crosstalk. Recent work from the Eaton lab now sheds new light on this process with the intriguing finding that the morphogen molecule Hedgehog (Hh) plays a critical role as a gut-derived circulating hormone in growth–diet coupling [3].

The *hedgehog* (*hh*) gene takes its name from the appearance of the larval cuticle of a *Drosophila* mutant identified in the late 70s [4]. Since then, Hh has been found to control cell–cell communication in many species, both in the context of healthy tissue organization and tumor formation. During larval development, Hh is produced in specific domains of imaginal discs — the tissues that form adult structures during metamorphosis, but grow during larval life — and instructs cells to undergo correct differentiation and morphogenesis. As a *bona fide* morphogen, Hedgehog forms gradients within the tissues where it is produced and the question of its secretion and transport currently stimulates an important area of research [5]. Interestingly, active Hh is a rather hydrophobic molecule and thus specific mechanisms have been proposed for Hh to pass through membranes and spread over tissues. One mechanism involves the loading of Hh onto lipoprotein particles [6], such as lipophorin (Lpp), which allows Hh to circulate in the larval hemolymph and potentially function as a hormone reaching remote targets [7]. Defining Hh as a new hormone requires that the source, function and target of this hormone are identified. By shutting down *hh* expression in different larval tissues, Rodenfels *et al.* [3] identified the enterocytes in the gut as the predominant source of Hh in the hemolymph. An insight into the hormonal function of Hh came from the observation that, when *hh* is silenced in the larval gut, larvae grow faster than controls; however, mature animals with silenced *hh* are not larger than controls because this faster growth rate is compensated by a shorter larval growth period. This suggested that gut-derived Hh functions to reduce larval growth rate and delay maturation. But what for? One clue comes from the observation that *hh* expression in the gut is significantly induced by starvation. Moreover, larvae lacking circulating Hh are more sensitive to starvation, while the starvation sensitivity of an *hh* null mutant larva can be efficiently suppressed by rescuing *hh* expression specifically in gut cells. Therefore, circulating Hh could participate in a protection mechanism against nutrient limitation by inducing a reduction in animal growth rate and an extension of the larval growth period.

But, a defect in either growth rate or developmental timing is observed depending on where reception of the circulating Hh signal is abrogated. Rodenfels *et al.* [3] bring three pieces of evidence that the fat body — a storage and endocrine organ that orchestrates the nutrient response [8,9] — is the target of circulating Hh for the control of growth rate (Figure 1): firstly, gut-derived Hh is required for triacylglycerol mobilization in the fat body under conditions of nutrient limitation; secondly, Hh, although not expressed in fat cells, is found in the fat body under conditions of starvation, and this accumulation disappears following knockdown of *hh* in the gut; and thirdly, the direct manipulation of Hh signaling in fat cells affects triacylglycerol mobilization, as described earlier [10,11], but also larval growth rate and starvation sensitivity. None of these manipulations alters the timing of maturation; consequently, animals enter maturation with incorrect sizes. These findings contrast with the absence of a size defect following manipulation of circulating Hh, suggesting that a distinct target tissue controls the timing of maturation. Indeed, activation of Hh signaling in the prothoracic gland — an endocrine part of the ring gland that produces the maturation hormone ecdysone — blocks ecdysone production and the transition to maturation. Conversely, this manipulation has no effect on the larval growth rate, confirming that Hh signaling independently controls the rate and duration of growth in separate

organs. Lowering Hh signaling in the prothoracic gland is not sufficient to induce precocious maturation, indicating that Hh signaling is one among many limiting inputs acting on ecdysone production in the prothoracic gland.

These findings are important for several reasons. First, they reveal a new role for Hh as a metabolic hormone facilitating long-distance cross-organ communication. Gut- and disc-derived Hh appear to serve distinct functions, although the mechanism responsible for this distinction is unclear. The lipid-associated form of Hh has both endocrine and paracrine effects in discs where it counteracts lipid-mediated inhibition of Hh signaling [7]. Furthermore, high levels of circulating Hh can act on discs too, suggesting that the distinction between the local and systemic effects is not absolute. Future research will help to clarify the functions associated with the different Hh sources.

Second, this work demonstrates a regulatory role for the gut in coupling larval growth with nutritional input. In the last decade, a number of epithelial receptors and transporters similar to the ones found in external sensing organs were shown to function in the gut to transduce signals controlling general metabolism and feeding in response to ingested nutrients [12]. Hh is among the first gut hormones identified in invertebrates to have a functional role in the nutrient response, suggesting functional conservation with vertebrate gut physiology. However, questions remain regarding the mechanisms by which Hh production and release are controlled by nutrients in gut enterocytes.

Third, this work demonstrates that Hh acts on two effector tissues and separately controls animal growth rate and duration. Previous studies have shown that larval growth rate is intimately linked to growth duration [13–15], therefore suggesting that Hh signaling could be part of the core coupling mechanism.

These exciting findings demonstrate the striking ability of animal models to renew classical concepts. After more than 30 years of work on deciphering its function as a tissue organizer, unexplored landscapes open up for Hh biology. A circulating, lipid-associated form of Sonic Hedgehog, one of the mammalian Hh isoforms, also exists [7], suggesting the possibility that Hh molecules in mammals have a conserved hormonal role that could account for the metabolic functions of mammalian Hh signaling [10,11,16].

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